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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/055,145	04/03/1998	DONALD P. WEEKS	3553-18	3535

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SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 05/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/055,145	WEEKS ET AL.	
	Examiner	Art Unit	
	David H Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,21-24,36-39,44,47,48 and 50-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,3,5,21,24,36,39,44,47,48,50-52,54-56 and 58-71* is/are rejected.

7)☒ Claim(s) *3,6,22,23,37,38,53 and 57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR § 1.114

1. A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 9 March 2004 has been entered.

2. Those rejections not specifically addressed in this Office Action are withdrawn in view of Applicant's amendments to the claims.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

4. Claims 1, 2, 4, 5, 7, 21, 24, 36, 39, 44, 47, 48, 50-52, 54-56, 58-65 and 66-68 remain rejected and claims 69-71 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reason of record as set forth in the last Office action mailed 10 March 2003. Applicant's arguments filed 9 March 2004 have been fully considered but they are not persuasive.

Applicant argues that the specification teaches one of skill in the art about significant structural features of the enzymes and provides a reference to several other known oxygenases that have similar subunit structures, and which can be referenced for guidance in the knowledge of what structural features are correlated with the biological activity of the oxygenase of the present invention. Applicant also argues that the December 13, 2002 Weeks Declaration provides additional evidence that by comparison to oxygenase structures known in the art, significant information regarding the structure of the claimed oxygenase can be determined and that the new Weeks Declaration, filed 9 March 2004, provides an even more detailed illustration and discussion of the structure of the claimed oxygenase as compared to known oxygenases (page 10 of the Remarks). This argument is not found to be persuasive because the presence of free-iron binding domains in a monooxygenase does not describe a dicamba monooxygenase, these structures of the enzyme describe a genus beyond dicamba degrading monooxygenases. At the time of Applicant's invention, Applicant had only described a single species of the claimed genus, as such Applicant could not describe the genus of dicamba degrading monooxygenases as broadly claimed by a single species as Applicant asserts, other than by function (See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), previously cited). The Weeks Declaration (2004) has been considered, but the evidence of isolation of other dicamba degrading monooxygenases after Applicant's invention is not deemed sufficient to overcome this rejection (see pages 8-10 of the Weeks Declaration of 2004).

Applicant argues that based on the alignment of multiple oxygenases, that mononuclear iron binding site highly conserved, particularly at selected positions, and therefore, one of skill in the art knows that modifications at these sites are not likely to be well tolerated if one wishes to maintain enzymatic activity and that it does not matter that this is not a unique active site within the oxygenase$_{DIC}$ it is a structure that is relevant to the functionality of a class of oxygenases including the oxygenase$_{DIC}$, regardless of the specific reaction catalyzed by the oxygenase, and it is information that one of skill in the art at the time of the invention can use to determine where in the protein modifications will be best tolerated (page 11 of the Remarks). This argument is not found to be persuasive because the issue is that mononuclear iron binding site(s) do not describe the genus of oxygenase$_{DIC}$ enzymes as broadly claimed. Applicant must describe those special technical features that describe oxygenase$_{DIC}$ enzymes. For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species, cannot be achieved by disclosing only one species within the genus. See also, MPEP § 2163 which states that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant argues that one of skill in the art will expect a protein that falls within a class of proteins to share some structural features with the other proteins in the class that allow the protein to have this general function. Applicant argues that the oxygenases will all bind to a substrate, and even though the substrate differs among oxygenases and therefore the specific amino acids that interact with substrate should be different, the substrate-binding region is expected to lie in a similar region of the protein among oxygenases. Applicant argues that in the case of Rieske non-heme iron-binding family of oxygenases (of which oxygenase$_{DIC}$ is a member), it is known that the portion of the substrate that is to be oxidized has to be in immediate proximity to the free iron atom that is a catalyst for the oxidation reaction, regardless of the identity of the substrate and that therefore, one of skill in the art would clearly avoid this site and the region in proximity to this site when making modifications. Applicant further argues that within the broad class of oxygenases, there are subclasses with even more highly defined structure-to-function relationships (page 12 of the Remarks). These arguments are not found to be persuasive because Applicant does not describe the substrate-binding region that describes oxygenase$_{DIC}$ enzymes as broadly claimed.

Applicant argues that even though oxygenases may be distinct in terms of primary sequence and substrate binding, one can readily use structural information about the class of enzymes to make determinations about where to modify a specific oxygenase (page 12, last line of the Remarks). This argument is not found persuasive for the reasons given supra.

Applicants argue that the attached new Weeks Declaration (2004) and submit that the data described therein provide even more evidence that the description provided in the specification, combined with the knowledge in the art at the time of the invention, is sufficient to allow one of skill in the art to selectively determine where modifications can be made in the protein that will avoid destroying the enzymatic activity of the protein, and that it is clear that up to 35% of the protein can easily be modified with the expectation that the protein will maintain biological activity (page 13, 1st paragraph of the Remarks). This argument is not found to be persuasive because Applicant's assertion is based on sequence similarity with other monooxygenases that do not degrade dicamba. It remains the Examiner's opinion that Applicant has failed to adequately describe those special technical features of $oxygenase_{DIC}$ enzymes that describe the invention as broadly claimed.

Applicant argues that the claims provide structure that distinguishes the variants of $oxygenase_{DIC}$ enzymes from other oxygenases by the limitations placed on the percent identity of the claimed oxygenase to the exemplified sequence (no other known oxygenase is even remotely close to the recited identity over the entire protein), and by the binding of the oxygenase to its specific substrate via the substrate binding region, or in the case of non-sequence based claims, by the recitation of specific structural/biochemical properties that are related to the function of the protein, and which have been used in the art to describe proteins for years (page 13, 2nd paragraph of the Remarks). This argument is not found to be persuasive for the reasons given supra. Essentially the description of the claimed invention as a monooxygenase that

degrades dicamba does not describe the genus of isolated DNA molecules as broadly claimed. Applicant has only described a single species within the claimed genus, and only describes other species by function.

Applicant argues that the structure of the enzyme is a significant factor in determining how the enzyme associates and dissociates with its substrate under various conditions and therefore, Km is another characteristic of the oxygenase of the present invention, which represents a known correlation between the structure and the function of an enzyme. Applicant argues that the structure of the enzyme significantly influences how it functions biochemically and therefore, Vmax is a characteristic of the oxygenase, which represents a known correlation between the structure and the function of an enzyme, and that the enzyme is described as catalyzing a specific enzymatic reaction, which is the functional characteristic related to the above-mentioned structural features (paragraph spanning pages 13-14 of the Remarks). It is unclear how this argument overcomes the instant rejection. Applicant states that the structure of the enzyme significantly influences how it functions biochemically, as such Applicant has not taught what structure that describes the claimed genus of oxygenase$_{DIC}$ enzymes.

Applicant argues that in contrast to the teachings of *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), the oxygenase claimed in the present claims is described in terms of a particular sequence or specific biochemical/physical properties; boundaries are set in the claims on what sequences are encompassed by the claims, e.g., via percent identity combined with a specific function or specific biochemical properties and importantly, the specification provides a description and

evidence of structural features that are associated with the activity of the enzyme and provides numerous examples of other oxygenases of similar type which can readily serve to inform the skilled artisan of structural conservation that is related to function. Applicant also argues that the specification also references other sources of dicamba-degrading bacteria from which similar oxygenases can be isolated (page 14, 4th paragraph of the Remarks). This argument is not found to be persuasive because in the same way that the description of the rat cDNA encoding insulin did not describe the human insulin cDNA, the description of the cDNA encoding the oxygenase$_{DIC}$ enzyme of SEQ ID NO: 4 does not describe isolated DNA molecules encoding other oxygenase$_{DIC}$ enzymes as broadly claimed. The structural features described in the instant specification also describe other monooxygenases comprising an iron-sulfur cluster that do not oxidize dicamba, as does a subunit molecular mass of about 40kD.

Applicant argues that the structural, biochemical and physical properties of the dicamba-degrading oxygenase provided by the specification are specific characteristics to describe what is not believed to be a widely varying genus of enzymes and that the claims are not simply directed to a cDNA encoding a dicamba-degrading oxygenase from any prokaryotic organism, or even from any bacterium, but rather to DNA encoding particular dicamba-degrading oxygenases from a particular source that has the specific structural and/or biochemical characteristics recited in the claims (page 15, 2nd paragraph of the Remarks). This argument is not found to be persuasive for the reasons given supra, Applicant has only described one species of the claimed genus of isolated DNA molecules encoding oxygenase$_{DIC}$ enzymes.

Applicants argue that the data, in the Weeks Declaration (2004), provides strong evidence that the DNA identified in the other bacterial strains does encode a dicamba-degrading oxygenase within the scope of the invention, because to conclude otherwise given the data is simply not statistically or scientifically sound in view of the data (page 16, 1st paragraph of the Remarks). Applicant also argues that as predicted, other species and genera of dicamba-degrading bacteria express dicamba-degrading oxygenases that fall within the scope of the claims can be readily identified using the exemplified oxygenase (page 16, 2nd paragraph of the Remarks). While the evidence in the Weeks Declaration (2004) may provide evidence that one of skill in the art could isolate other DNA molecules encoding dicamba-degrading oxygenases from other bacteria, it does not overcome the issue of written description in the instant case.

Another issue not specifically addressed in Applicant's response is at claim 2, the claim to a fragment of SEQ ID NO: 4 that catalyzes the oxidation of dicamba has not been adequately described because Applicant does not describe fragments that having this function.

5. Claims 1, 2, 4, 5, 7, 21, 24, 36, 39, 44, 47, 48, 50-52, 54-56, 58-65 and 66-68 remain rejected and claims 69-71 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the DNA molecule of SEQ ID NO: 3, DNA molecules encoding the dicamba-degrading oxygenase of SEQ ID NO: 4, methods of using said DNA molecules and plants comprising said molecules, does not reasonably provide enablement for any DNA molecule encoding a dicamba-degrading oxygenase within the scope of the instant claims. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is repeated for the reason of record as set forth in the last Office action mailed 10 March 2003. Applicant's arguments filed 9 March 2004 have been fully considered but they are not persuasive.

Applicant's amendments to claims 2 and 5, for example, have addressed the issue raised in the prior art and addressed in Applicant's arguments on page 17 to page 18, 3rd paragraph of the Remarks. The inclusion of a specific function overcomes the issue raised in the art by Siminsky *et al.*

Applicants argue that they have provided further evidence of the existence of oxygenases from other dicamba-degrading bacteria that fall within the scope of the claims and that variants of this enzyme having the same catalytic activity are predictably expected to have the same uses. Applicant further argues that the specification has provided sufficient guidance to those of skill in the art to be able to predictably make and use a dicamba-degrading oxygenase as claimed in the current claims (page 19, 1st paragraph of the Remarks). This argument is not found to be fully persuasive because Claim 1 is directed to any isolated DNA molecule encoding a dicamba-degrading oxygenase of about 40kD, comprising a iron-sulfur cluster and catalyzes the oxidation of dicamba to 3,6-dichlorsalicylic acid, and claim 2 is directed to an isolate DNA molecule encoding said oxygenase which is at least about 65% identical to the amino acid sequence of SEQ ID NO: 4. Applicant states that the structure of the enzyme is a significant factor in determining how the enzyme associates and dissociates with its

substrate under various conditions and therefore, Km is another characteristic of the oxygenase of the present invention, which represents a known correlation between the structure and the function of an enzyme and that the structure of the enzyme significantly influences how it functions biochemically and therefore, Vmax is a characteristic of the oxygenase, which represents a known correlation between the structure and the function of an enzyme, and that the enzyme is described as catalyzing a specific enzymatic reaction (paragraph spanning pages 13-14 of the Remarks). To this point, the Examiner argues that the structure of an enzyme is integral to its function, and that Applicant has only provided guidance to make and use an isolated DNA molecule encoding the amino acid sequence of SEQ ID NO: 4. The art teaches that cytochrome P450 enzymes interact with other proteins, in particular reductases that donate an electron during the reaction, and are associated with membrane structures within the cell (Donaldson *et al* 1991, Plant Physiology 96:669-674, see Figure 1 on page 670). Hence, one of skill in the art must take into consideration structures of a P450 enzyme that are not only critical to substrate binding and metabolism, but also to association with other proteins involved in the transfer of electrons and associations within the membrane. Given the breadth of the claims, it remains the Examiner's opinion that it would have required undue trial and error experimentation by one of skill in the art at the time of Applicant's invention to make and use the genus of isolated DNA molecules as broadly claimed.

Applicant argues that the Weeks Declaration (2004) shows that given the description provided in the instant application and given the knowledge of the structure

of oxygenases in the art, one of skill in the art can readily modify the $oxygenase_{DIC}$ gene of the present invention to cause directed changes in the amino acid sequence of the $oxygenase_{DIC}$ enzyme without destroying the enzymatic activity of the protein in vivo, and that the Declaration demonstrates that oxygenases that fall within the scope of the claims can be identified in other dicamba-degrading bacteria (page 19, 2nd paragraph of the Remarks). This argument is not found to be persuasive be the Weeks Declaration (2004) does not support the breadth of the instant claims as Applicant asserts. Said declaration only teaches encoded amino acid sequence that are 90% or 99% identical from amino acids 15-326 of SEQ ID NO: 4. This evidence does not support the bread of the claimed invention. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970) which teaches "That paragraph (35 USC 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.".

Another issue not specifically addressed in Applicant's response is at claim 2, the claim to a fragment of SEQ ID NO: 4 that catalyzes the oxidation of dicamba has not

been adequately enabled because Applicant does not taught how to make and use fragments that having this function within the full breadth of the claims.

Allowable Subject Matter

6. Claims 3, 6, 22, 23, 37, 38, 53 and 57 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Claims 1, 2, 3, 5, 21, 24, 36, 39, 44, 47, 48, 50-52, 54-56 and 58-71 are rejected.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (571) 272-0804. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (571) 272-0547.

David H. Kruse
AV 1638

David H. Kruse, Ph.D.
24 May 2004